

Final Key Questions and Background

Testosterone Testing

Introduction

Testosterone is the main androgen (male hormone) secreted by the testes, and testes are the major source of circulating androgens. A condition called hypogonadism is characterized by lower than physiological levels of testosterone (androgen deficiency) and less than a normal number of spermatozoa. However, low testosterone does not by itself justify a diagnosis of hypogonadism or the need for testosterone replacement treatment. The term hypogonadism denotes decreased functioning of the gonads (testes in males). Clinical (symptomatic) hypogonadism occurs in all degrees, from profound hypogonadism as is seen with castration or severe hypopituitarism, to milder degrees such as may be seen with partial hypopituitarism, hyperprolactinemia, or various other types of suppression of the hypothalamo-pituitary-gonadal axis. In some cases hypogonadism can be clearly associated with a pathological process, such as in hypopituitarism or gonadal dysgenesis. In other cases it appears to be a functional response, as in suppression of the hypothalamo-pituitary-gonadal axis in chronic opioid exposure. In yet other cases, an apparent decline in gonadal function, as may occur gradually with aging, may not be a clearly pathological process. Age-related depletion of testosterone, sometimes called *late onset hypogonadism* (LOH), affects approximately 5% of middle-aged to elderly men.

Low testosterone has been found to be associated with various chronic diseases and conditions such as osteoporosis, obesity, type 2 diabetes, ischemic heart disease, hypercholesterolaemia, and hypertension, but causal mechanisms are unclear with the exception of osteoporosis. Low testosterone is sometimes implicated in male factor infertility, but male factor infertility can also be caused by numerous other factors and is often idiopathic. A variety of other conditions, genetic factors, exposures, and treatments are thought to potentially diminish testosterone levels.

While certain hypogonadal syndromes present with clear-cut clinical signs, such as delayed puberty or pituitary lesions, milder degrees of putative hypogonadism are typically more subtle in presentation. Symptoms such as loss of libido, erectile dysfunction, fatigue, loss of muscle mass, and mood changes have been associated with lower testosterone levels, but not all men with low testosterone have symptoms and the unspecific nature of these symptoms means that symptoms do not always indicate low testosterone.

Testosterone testing is multifaceted. When low testosterone is suspected, serum total testosterone is initially measured, followed by measurement of free testosterone or bioavailable testosterone (BAT). Additional laboratory tests may be required to characterize the etiology of hypogonadism as primary (testicular failure) or secondary (defect of the hypothalamus or pituitary). In certain clinical situations, genetic testing is also appropriate to identify etiology.

Practice guidelines recommend *against* routine screening for low testosterone in asymptomatic individuals. For individuals with symptoms suggestive of low testosterone, it may be advisable to first treat potential causes for the symptoms other than low testosterone. Other conditions that can produce

the same symptoms include obesity and physical inactivity. However, The Endocrine Society guidelines do recommend testing in situations where the prevalence of testosterone deficiency is relatively high. High prevalence situations are identified as:

- Sellar mass, radiation to the sellar region, or other diseases of the sellar region (of the pituitary gland)*
- Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids and opioids*
- HIV-associated weight loss*
- End-stage renal disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low trauma fracture, especially in a young man*
- Type 2 diabetes mellitus

*According to the Endocrine Society, testing may be reasonable even in the absence of symptoms.

The technologies that serve as reference standards for measuring total testosterone, free testosterone, and BAT are not practical for use in typical practice settings. The accuracy of commercially available assays for total testosterone is variable for individuals whose concentrations fall below the normal reference range. Universally accepted methods of measuring or calculating free testosterone and BAT do not exist. Furthermore, there is no consensus on either the cutoff value for normal levels, or whether cutoff values should be age-related.

Treatments that are effective in raising testosterone levels are available. Practice guidelines recommend treatment of hypogonadism to improve well-being, sexual function, and bone health, except in patients with breast cancer, prostate cancer, or high risk of prostate cancer. Guidelines caution against routinely offering testosterone therapy to older men. It is also not considered useful to test testosterone levels in men who are acutely ill. The ability of testosterone treatment to improve patient-important outcomes, including reduction in osteoporotic fracture, has not been well-established. There is also uncertainty about the adverse effects of testosterone replacement therapy on mortality, cardiovascular disease, incident prostate cancer, and problems such as sleep apnea. Repeat testing at 3 to 6 months following initiation of therapy and annually thereafter is recommended.

Policy Context

The Centers for Medicare & Medicaid (CMS) has no National Coverage Determination (NCD) applicable to testosterone testing or treatment of hypogonadism. The CMS the Medicare Benefit Policy Manual includes no statements on testosterone testing or hypogonadism. A number of commercial assays for testosterone testing have been cleared for marketing by the FDA and are described in recent decision summaries as being appropriate for the diagnosis and treatment of disorders involving androgens, including primary and secondary hypogonadism. The United States Preventive Services Task Force (USPSTF) has issued no recommendations on testosterone testing.

Considerable controversy and uncertainty exist concerning the diagnostic criteria for hypogonadism, techniques for measuring testosterone levels, the cutoff value for normal testosterone, the benefits and harms of treatment, and the optimal interval for repeat testing. In recent years new topical formulations of testosterone have been developed and marketed, obviating the requirement of administration by intramuscular injection and encouraging broader application of testosterone replacement therapy for

milder and potentially nonpathological forms of hypogonadism. A review of the evidence on the risks and benefits of testing, taking into account what is known about the benefits of treatment, is warranted to guide coverage policy on testosterone testing.

Scope of This HTA

Populations: Adult men

Interventions: Measurement of circulating total, free, or bioavailable testosterone as an initial assessment of possible hypogonadism

Comparators: Investigation and clinical management of symptoms or health problems without the use of testosterone testing

Outcomes: Outcomes such as: symptom improvement; general health outcomes (e.g., osteoporosis, chronic disease, mortality); clinical management decisions; potential harms resulting from testosterone treatment decisions; cost and cost-effectiveness.

Key Questions

1. Is there evidence that testosterone testing improves outcomes?
 - 1a. Does the impact on outcomes vary according to age, race/ethnicity, baseline testosterone levels, treatment status, or clinical history?
 - 1b. What is the minimum interval required to assess a change in testosterone status in untreated and treated individuals?
2. What are the potential harms of testosterone testing, including potential subsequent harms resulting from treatment decisions?
3. What are the costs and cost-effectiveness of testosterone testing?

For more information about this technology review and the Washington State Health Technology Assessment program, visit www.hca.wa.gov/hta.